From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/010737	07.04.2004	07.04.2003

International Patent Classification (IPC) or both national classification and IPC
C07D213/79, C07D213/80, C07D401/12, C07D403/12, C07D413/12, C07D417/12, A61K31/423, A61K31/428,

Applicant
KALYPSYS, INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/010737

10/552358

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,29-32,59-62,92-95 (all part),97-119

because:

☒ the said international application, or the said claims Nos. 97-119 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 1,29-32,59-62,92-95 (all part) are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-96,100-115,121-124
	No:	Claims	1,97-99,116-120
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-124
Industrial applicability (IA)	Yes:	Claims	1-96,120-124
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Claims 97-119 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Moreover, it is noted that the application refers to "prodrugs" and "metabolites". These terms are functional definitions which attempt to define a chemical compound in terms of a result to be achieved without giving a specific technical guidance for the selection of the suitable derivatives in the description and without proven general knowledge to show which derivatives in this specific case are suitable prodrugs. The term could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants. In such a situation, when the invention cannot be carried out over the whole claimed area without imposing an undue burden on the skilled person, the disclosure may be considered insufficient, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims. Therefore, the said terms have not been searched and do not part form part of the examined current subject-matter.

Re Item V.

The following documents are referred to in this communication:

(A) J. Med. Chem. 1971, vol. 14, no. 4, pages 369-370
(B) US 4206117 A
(C) WO 0230895 A
(D) WO 0064888 A
(E) EP 1067109 A
(F) WO 9728149 A

Novelty

The current general formula I appears not to be novel in the sense of Article 33(2) PCT since (A)-(C) disclose specific compounds falling within its scope. However, the current part overlapping with (D) appears to be a novel selection of (D) and the current compounds essentially differ from those of (E) and (F) on account of the O-$(CH_2)_3$-N-linker.

Inventive Step

The problem underlying the current application is considered to be the provision of further PPAR-modulators which are useful for the treatment of e.g. atherosclerosis. (C) appears to be the closest prior art disclosing compounds which fall within the current general formula and have the desired activity. An inventive step could therefore only be acknowledged for a delimited subject-matter with an improved effect which in the light of the closest prior art is surprising. Such an unexpected effect appears not to be present in the application documents so that the current subject-matter at present does not satisfy Article 33(3) PCT.

Industrial Applicability

For the assessment of the present claims 97-119 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Items VII. and VIII.

It is noted that claim 95 appears not to be clear in the sense of Article 6 PCT since "KP001" etc. are no generally known definitions or names and, moreover, the description does not unambiguously assign specific compounds to these expressions: The headings in table 1 (pp 22-30) are unreadable but apparently lack the definition of 3 substituents, and the following pages define one substituent without specifying the other 2-3 missing substituents. Concerning the opinion given above it is preliminarily assumed that claim 95 in fact is a dependant claim of claim 1.